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(71) Applicant *(for all designated States except US)*: TOP GOLD PTY., LIMITED [AU/AU]; c/o Anderson & Brian, 23/818 Pittwater Road, Dee Why, NSW 2099 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : PAPANDREA, Ralph, Anthony [AU/AU]; 10 Seaview Parade, Collaroy, NSW 2097 (AU). THOMAS, Richard, Edward [AU/AU]; 14 Parnell Street, Killara, NSW 2071 (AU).

(74) Agent: ERNST, Ian, Thomas; Shelston Waters, 55 Clarence Street, Sydney, NSW 2000 (AU).

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(54) Title: SUSTAINED RELEASE ANALGESICS

(57) Abstract

A composition comprising at least one analgesic, preferably paracetamol, in a dose form adapted for sustained release and in a concentration selected to provide an analgesically effective dose at a substantially constant dose rate over at least 8 hours. The administered dose rate for paracetamol is preferably from 150 - 400 mg/hr.

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Title: "SUSTAINED RELEASE ANALGESICS"

TECHNICAL FIELD

This invention relates to the preparation of analgesics in sustained release form. More particularly, it relates to the preparation of non-opioid analgesic agents in a sustained release form.

BACKGROUND ART

The term analgesic encompasses a broad range of pharmaceutical compounds that fall into three main categories: opioid (or narcotic) analgesics; non-steroidal anti-inflammatory agents (NSAIDs); and non-opioid analgesics. Included among the opioids are the opium alkaloids and their semi-synthetic derivatives (such as meperidine and methadone) that have somewhat different structures but similar effects, and the "opiopeptins" (such as ß-endorphin and the enkephalins). Opioid analgesics produce pain relief and sedation by

way of a diverse range of biochemical pathways involving one or more classes of opioid receptors. Typical examples of the analgesics that fall within this class are morphine and codeine. Opioid analgesics have traditionally been referred to as 'narcotic analgesics' to distinguish them from the antipyretic (or coal tar) analgesics such as aspirin, phenacetin and paracetamol (acetaminophen). Aspirin is now classified as an NSAID.

NSAIDs encompass a broad range of pharmaceutical drugs which share the capacity to suppress the signs and symptoms of inflammation. It is this mode of action which makes these drugs particularly useful in the management of disorders in which pain is related to the intensity of the inflammatory process. NSAIDs are widely used for the treatment of inflammatory disorders of muscular, skeletal, vascular and connective tissues, including such conditions as arthritis, bursitis, postpartum states and dental pain, to mention a few. These drugs are heterogenous in chemical structure but have in common the ability to inhibit prostaglandin synthesis. A well-known example of the analgesics which fall within this class is aspirin.

Non-opioid, non-NSAID, analgesics encompass a small range of pharmaceutical compounds of which phenacetin and paracetamol (acetaminophen) are well-known examples. These pharmaceuticals are particularly useful for the treatment of mild to moderate pain where

an anti-inflammatory effect is not necessary. Their use includes the treatment of headaches, myalgia, postpartum pain and other medical conditions that require mild pain relief.

Of the non-opioid analgesics, paracetamol (acetaminophen) is particularly useful for treating patients suffering from mild pain who are allergic or otherwise intolerant to aspirin or other NSAIDs. For example, paracetamol can be used for treating patients with a history of peptic ulcers or patients where bronchospasm is precipitated by NSAIDs such as aspirin.

The dosage of analgesics, in general, depends on the type and intensity of the pain and the particular analgesic agent used. For example, 500-1000 mg of paracetamol is normally used to combat mild pain and fever in adult humans. When administered orally this drug has a half-life of approximately two to three hours in the body. Accordingly, it has hitherto been practiced to re-administer the drug at intervals of 4 to 6 hours to maintain an effective concentration.

It has been hitherto generally believed that the return of pain as the concentration of analgesic diminished, was due solely to the wearing off of the drug effect. It has now been found, at least for some patients, that this assumption is incorrect. In these patients, blood levels of paracetamol fall rapidly as the drug is eliminated. This leads to a rapid pain

"rebound" effect as the natural analgesic agents in the body do not have sufficient time to take over and re-assert their action before the introduced analgesic agents are eliminated. To overcome this rapid pain "rebound" effect, shorter administration times between dosages are often required. This may result in deleterious side effects to the patient or may cause inconvenience, especially at night. In addition to their effect on natural analgesic agents, drugs such as paracetamol, when introduced at high doses, may also cause disorientation, excitement and dizziness.

It is an object of the present invention to provide a means for avoiding, or at least ameliorating, the above-discussed disadvantage of analgesics and, more particularly, of non-opioid analgesics.

DISCLOSURE OF THE INVENTION

The present invention relates to a composition comprising at least one analgesic in a dose form adapted for sustained release and in a concentration selected to provide an analgesically effective dose at a substantially constant dose rate over at least 8 hours.

BEST MODE FOR CARRYING OUT THE INVENTION

The invention will now be more particularly described by way of example only.

The analgesic which is adapted for substained release can be selected from the group consisting of opioid analgesics, non-steroidal anti-inflammatory

analgesic and non-opioid analgesics. Preferably the analgesic is a non-opioid analgesic such as paracetamol. Analgesics may also be adapted in a substained release form with other analgesics or medications such as doxylamine. A typical combination used in the present invention consists of paracetamol and codeine or paracetamol, codeine and doxylamine.

In a preferred embodiment of the invention, paracetamol is selected as the analgesic. Hitherto, it has been usual to administer paracetamol in dose units of up to 500 mg per unit and to administer up to two such dose units (1000 mg total dose) each 4 hours.

According to one embodiment of the present invention, paracetamol is provided in a sustained release form which provides a substantially constant dose rate of from 150 - 400 mg/hr sustained for at least 8 hours. This means that a total dose of, for example, from 1200 to 3200 mg is administered by means adapted for constant rate release over 8 hours. The 1200 to 3200 mg can be in one dosage unit or can be in two dosage units suitable to be administered together and each containing from 600 to 1600 mg adapted for release over 8 or more hours, and so forth.

In a more highly preferred embodiment, the constant dose rate is from 200 to 300 mg/hr for at least 8 hours and more preferably about 240 to 260 mg/hr.

It will be appreciated that the constant dose rate

in mg/hr for other non-opioid analgesics to give an analgesically effective rate may be greater or less than 150 - 400 mg/hr but will in general be about 1.5 to 3 times as great as the amount normally previously administered without sustained release.

The dosage form which is adapted for substained release preferably releases the analgesic at a substantially uniform rate over a period of at least 8 hours and preferably from 8 to 12 hours or more preferably over a period of from 8 to 24 hours. However the period of substained release is dependent on the analgesic used and the requirement of the patient. Any suitable dosage form providing release of the analgesic over a long period and preferably at a uniform rate of release may be used.

The present invention further relates to a composition comprising at least one analgesic having a dose unit in the range of from 500 mg to 1500 mg and in a dosage form adapted for substained release wherein said composition further comprises an analgesic adapted for rapid release.

As herein used, the term "rapid release" means that the analgesic is released quickly for example in less than 1 hour, more preferably in less than 30 minutes.

As with analgesics in a dose form adapted for substained release, analgesics in a dose form adapted for rapid release can be selected from the group

consisting of opioid analgesics, non-steroidal anti-inflammatory analgesic and non-opioid analgesic. Preferably, the analgesic is a non-opioid analgesic such as paracetamol. Analgesics in a sustained release form may be combined with other analgesics or medications such as doxylamine. A typical combination used in the present invention consists of paracetamol and codeine or paracetamol, codeine and doxylamine.

The present invention also relates to a method for avoiding the pain rebound effect comprising administering an analgesically effective amount of a composition comprising at least one analgesic from a dosage form adapted for substained release at a constant rate over at least 8 hours.

The "rebound" phenomenon is not new as far as some other drugs are concerned but has not been previously linked with the pharmacokinetic properties of analgesic drugs. For example, many patients who use short-acting hypnotics, such as temazepam, experience rebound reactions ranging from extreme wakefulness to, in some cases, an outright panic reaction. Such reactions can be minimized if the patient is given a long-life hypnotic such as nitrazepam.

Although pain-rebound has been described with analgesic use, the existence of the phenomena has hitherto remained controversial and no evidence exists to determine whether the phenomena, if it exists, is due

to a property of the patient or the drug, and, if the latter, whether the attribute is due to a pharmacodynamic or pharmacokinetic property. A particular advantage resulting from the present invention is that analgesics in a sustained release form remain in the body and, more particularly, the blood, for longer periods of time, and taper off gradually as the sustained-releasing means wears out. This is particularly advantageous as it allows natural endogenous analgesic substances in the patient's body to re-assert their action, thereby reducing the so-called pain "rebound" effect which is seen with non-sustained release analgesic preparations.

Methods of applying a sustained release composition broadly fall into three categories namely transdermal, oral and implantation means.

Transdermal administration of a drug to a patient may take place in a number of ways. A typical example is the use of pharmaceutical patches that contain drugs for transdermal administration. Oral sustained release formulations of drugs include incorporation in slow release reservoirs or by any other means known in the art. Sustained release by implantation of a drug generally occurs at the sub-dermal level where the drug to be released is packaged in a slow release device. Typically, methods of sustaining the release of a product are well-known in the art and, as such, any recognized means of slowing the release of an analgesic

may be used in the present invention.

Preferred formulations include microcapsules coated with agents such as ethylcellulose incorporating waxes such as paraffin wax, with our without an overlay of an enteric coating such as cellulose acetate. Another preferred approach is the preparation of microspheres. Although the latter have usually achieved an incorporation level of no better than 50%, incorporation of 80-90% can now be achieved. Microspheres can also be formulated to provide a burst effect in which a portion of the drug is released quickly and the remainder over a prolonged period.

More specifically, oral means for sustaining the release of an analgesic may generally be categorized in two classes namely encapsulation or in tablet form.

CAPSULE FORMULATION

There are at least three general approaches which may be employed in capsule formulation.

The first approach is to combine a physical mixture or a form of granulation of the active ingredients and a suitable hydrophilic polymer. The combination of powder can then be dispensed in a conventional gelatin capsule. The same approach may be employed, with only a few modifications in the formulation of tablets.

The second approach is to produce suitable particles of the active ingredient(s) and to deposit a polymeric coating on them. The coating material may be

chosen such that an enteric effect is obtained or that release will be more uniform throughout the whole of the gastrointestinal tract. This technique is generally referred to as microcapsule formation.

The third approach is related to microcapsule formation and is the production of microspheres. Microspheres are solid particles of a matrix material through which the active ingredients are uniformly or non-uniformly dispersed. Uniform distribution is technically easier to attain, but calculated non-uniform distribution may lead to better attainment of zero-order release. A variety of synthetic or natural materials can be employed as the matrix.

APPROACH 1:

(POWDER MIXTURE (GRANULATION) WITH A HYDROPHILIC POLYMER)

This approach employs a physical mixture (or some form of granulation) of the active ingredients with a suitable hydrophilic polymer. The combination of powders is dispensed in a conventional gelatin capsule. The expected mechanism(s) of release is diffusional release of the relatively water-soluble active ingredients through the hydrated and presumably swollen polymer matrix, and drug release due to biodegradation of the matrix.

APPROACH 2: (MICROCAPSULE FORMATION)

Techniques to produce microcapsules are well known in the art. Basically, the techniques involve the

deposition of a polymer coating onto core particles of drug. The release characteristics (time to release, pH dependency etc) can be regulated by the type of polymer used or the thickness of the coating applied Accurate control of the release pattern usually depends critically on the integrity of the polymer coating.

Pan-coating is a simple means of depositing the coating, but requires large (at least 0.5 mm diameter) spherical particles to achieve a good rolling action in the pan and to avoid aggregation. This can be achieved by the attrition of large particles in suitable mechanical equipment For example, one particular technique employs spheronization in which 20-40 mesh particles of paracetamol are sprayed with alcoholic PVP, dusted with fine powdered drug and rolled dry in a stream of cold air. The process is repeated until spherical particles of the required size and shape are obtained. The cores can be polymer-coated to yield sustained release. The process has the advantage that the cores have a very high content of active ingredient, especially compared to techniques in which granules are prepared using conventional binders such as microcrystalline cellulose or carboxy-methylcellulose.

An alternative method may involve coating spherical cores with ethylcellulose. This method may be accomplished by dissolving the polymer in cyclohexane at 80-81°C, dispersing the cores in a vigorously stirred

solution and then gradually cooling the liquid. The polymer separates as a liquid coacervate and deposits onto the cores which are prevented from aggregating by stirring. At 20-25°C, the microcapsules are filtered and dried. The microspheres can be made more hydrophobic by incorporating waxes (e.g. paraffin) in the cyclohexane with the ethylcellulose.

Paracetamol cores coated with ethylcellulose can also be coated with cellulose acetate phthalate as an enteric coat on a non-disintegrating particle. Cores coated in this way will release very slowly in an acidic environment and faster (but relatively constantly) in an alkaline medium.

APPROACH 3: (MICROSPHERE FORMATION)

The formation of microspheres ladened with active drug is well known in the art. For example, actives can be combined with waxy monoglycerides, in poly (hydroxy butyric acid) and in gelatin to name a few means of forming microspheres. An alternative approach is to produce 30 mesh polystyrene beads which can be expanded and made more porous by soaking in n-pentane prior to boiling in water. The beads are able to take up about 20% by weight of paracetamol by soaking in alcoholic solution. When administered to a patient about 65% of the load is released over a relatively short period of time (e.g. 30 to 60 mins) and the remainder over a 24 hour period.

Paracetamol may be incorporated in egg albumin microspheres. In this instance, the albumin matrix may be hardened by employing both thermal denaturation and cross-linking with glutanaldehyde. The microspheres produced might then be pan-coated with polymethacrylate to prolong the release of the active without compromising the bioavailability of paracetamol.

Paracetamol might also be entrapped in microspheres by the drug suspending in a viscous solution of sodium alginate and extruding the product into a solution of calcium ions to produce spherical beads of calcium alginate which contain the entrapped drug. The beads may then be collected and dried to form a delivery system which results in prolonged release. A similar technique utilizes entrapment of active drugs in chitosan beads gelled with sodium tripolyphosphate. Such methods readily allow the incorporation of 80-90% w/w of drug in the beads and result in prolonged release of the drug. The use of such systems can prolong drug release for about 6 hours in an acidic medium.

TABLET FORMATION

Most of the comments made in approach 1 above are pertinent to tablet formation. Microspheres and Microcapsules would not desirably be presented as tablets since compression would result in crushing of the sphere or cracking of the rate-controlling membrane of a microcapsule. If compression is used to decrease

the volume of the active ingredient(s) by powder densification then it is important that any hydrophilic polymer combined with the active is compressible. Further, the formulation may require the addition of binding, lubricating and flow-enhancing excipients. A direct compression vehicle (e.g. calcium phosphate dehydrate or hydroxyapatite) may also be added to the polymer and drug mixture or perhaps to the drug(s) alone.

In the case of a paracetamol dose form according to the invention it is preferred to provide each adult with 2 dose units. Each dose unit contains from 600 mg to 1,600 mg of paracetamol (preferably 1000 mg) so that the total dose administered with 2 dose units is 1200 to 3200 mg of paracetamol. Each dose unit is adapted to release the paracetamol at 75 - 200 mg/hr over 8 hours, thus providing a total administered dose rate of 150 - 400 mg/hr for 8 hours.

More preferably the dose units are adapted to provide 100 - 150 mg/hr and more preferably 125 mg/hr per dose unit. 2 dose units taken together then provide around 200 - 300 mg/hr of paracetamol per hour and preferably 250 mg/hr for 8 hours.

Correspondingly, adjustment can be made for doses adapted for release over a longer period with due regard for safety in the event of overdose.

The invention described is suitable for treating a wide range of pain conditions but is particularly suited

for chronic pain such as that associated with osteoarthritis and similar disorders of the joints or muscles including chronic tension headache. It may also be used alone, or in association with other analgesic therapy, in the treatment of malignant disorders or where other chronic analgesic therapy is contraindicated. In all these cases, pain rebound can be a problem when short-acting analgesic formulations are used. In a preferred example, two sustained-release paracetamol dose units, each containing 750 - 1000 mg (alone or admixed with other actives), are administered twice daily. Because of the low incidence of adverse effects to therapeutic doses of paracetamol, the dosage regimen described above can, in most cases, be used for prolonged periods.

Uses of the present invention are not to be restricted to human beings. Rather, formulations containing analgesic compounds in sustained release forms may be administered to any mammal in need thereof. The dosage administered will depend on the analgesic and the mammal to which a formulation is administered. Formulations of sustained release analgesics should be prepared according to recognised art and dosage levels.

CLAIMS:-

1. A composition comprising at least one analgesic in a dose form adapted for substained release and in a concentration selected to provide an analgesically effective dose at a substantially constant dose rate over at least 8 hours.

2. A composition according to claim 1 wherein the analgesic is paracetamol, the dose unit contains at least 600 mg of paracetamol and the constant dose rate is from 75 - 400 mg/hr.

3. A composition according to claim 1 or claim 2 wherein the analgesic is paracetamol and the constant dose rate is from 200 - 300 mg/hr.

4. A composition according to claim 2 wherein the dose form has from 750 mg to 1500 mg of paracetamol.

5. A composition according to claim 1 wherein the dosage form is adapted for substained release of the dose unit over a period of from 8 to 24 hours.

6. A composition according to claim 5 wherein the dosage form is adapted for substained release of the dose unit over a period of from 8 to 12 hours.

7. A composition according to any one of the preceding claims further comprising an analgesic adapted for rapid release.

8. A composition according to any one of the preceding claims wherein the analgesic adapted for substained release is selected from the group consisting of opioid

analgesics, non-steroidal anti-inflammatory analgesic and non-opioid analgesics.

9. A composition according to claim 8 wherein the analgesic adapted for substained release is a non-opioid analgesic.

10. A composition according to claim 8 or 9 wherein the analgesic adapted for substained release is paracetamol.

11. A composition according to claim 8 wherein the analgesic adapted for substained release is a mixture of paracetamol and codeine.

12. A composition according to claim 8 wherein the analgesic adapted for substained release is a mixture of paracetamol, codeine and doxylamine.

13. A composition according to claim 7 wherein the analgesics adapted for rapid release is selected from the group consisting of opioid analgesics, non-steroidal, anti-flammatory analgesic and non-opioid analgesics.

14. A composition according to claim 13 wherein the analgesic adapted for rapid release is a non-opioid analgesic.

15. A composition according to claim 13 or 14 wherein the analgesic adapted for rapid release is paracetamol.

16. A composition according to claim 13 wherein the analgesic adapted for rapid release is a mixture of paracetamol and codeine.

17. A composition according to any one of the preceding claims wherein the dosage form is an oral formulation.

18. A composition according to claim 17 wherein the oral formulation is selected from the group consisting of tablets, capsules, microcapsules, microspheres and liquid formulations.

19. A pharmaceutical composition for treating headaches and the like comprising a pharmaceutical carrier and a therapeutically effective amount of a composition according to any one of claims 1 to 18.

20. A method for avoiding pain rebound comprising administering a therapeutically effective amount of a composition according to any one of claims 1 to 18 and/or a composition according to claim 19.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU93/00088

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.[5] A61K 31/165 // 9/22 9/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 9/- 31/165

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT: KEYWORDS: Analgesic, Paracetomol, NSAID sustained release, Controlled release, Prolonged release
CAS ONLINE:KEYWORDS:Analgesic, Paracetomol, NSAID sustained release, Controlled release, Prolonged release

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP 0263083 (VALDUCCI, ROBERTO) 6 April 1988 (06.04.88) Column 1 lines 47-54, Examples 2, 3	1-6,8-10,17-20
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X	AU 81862/91 (FARSON AG) 23 January 1992 (23.01.92) Page 3 lines 16-21, page 4 lines 2-10 Examples	1,5-8,13,17-20
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 May 1993 (14.05.93)	26 MAY 1993 (26.05.93)
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929	Authorized officer JOHN HANSON Telephone No. (06) 2832262

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU93/00088

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT
Information on patent family memb.

International application No.
PCT/AU93/00088

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU
CONTINUED

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		FI	842400	FR	2547498	GB	2141338
		HK	955/90	IT	1200967	LU	84962
		NL	8302842	NO	842362	NZ	204708
		PH	17827	SE	8304393	SG	809/90
		US	4571333	ZA	8305591	US	4803079
							END OF ANNEX